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☐ 1: Imaoka S, Hashizume T, Funae Y.

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Localization of rat cytochrome P450 in various tissues and comparison of arachidonic acid metabolism by rat P450 with that by human P450 orthologs.

Drug Metab Pharmacokinet. 2005 Dec;20(6):478-84.

PMID: 16415532 [PubMed - indexed for MEDLINE]

☐ 2: Kalsotra A, Cui X, Anakk S, Hinojos CA, Doris PA, Strobel HW.

Related Articles, Links



Renal localization, expression, and developmental regulation of P450 4F cytochromes in three substrains of spontaneously hypertensive rats.

Biochem Biophys Res Commun. 2005 Dec 9;338(1):423-31. Epub 2005 Aug 25.

PMID: 16182239 [PubMed - indexed for MEDLINE]

☐ 3: Parmentier JH, Lavrentyev EN, Falck JR, Capdevila JH, Malik KU.

Related Articles, Links



Evaluation of cytochrome P450 4 family as mediator of phospholipase D activation in aortic vascular smooth muscle cells.

Life Sci. 2005 Jul 15;77(9):1015-29.

PMID: 15964316 [PubMed - indexed for MEDLINE]

☐ 4: Nithipatikom K, Gross ER, Endsley MP, Moore JM, Isbell MA, Falck JR, Campbell WB, Gross GJ.

Related Articles, Links



Inhibition of cytochrome P450 omega-hydroxylase: a novel endogenous cardioprotective pathway.

Circ Res. 2004 Oct 15;95(8):e65-71. Epub 2004 Sep 23.

PMID: 15388642 [PubMed - indexed for MEDLINE]

☐ 5: Xu F, Falck JR, Ortiz de Montellano PR, Kroetz DL.

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Catalytic activity and isoform-specific inhibition of rat cytochrome p450 4F enzymes.

J Pharmacol Exp Ther. 2004 Mar;308(3):887-95. Epub 2003 Nov 21.

PMID: 14634044 [PubMed - indexed for MEDLINE]

☐ 6: [Stec DE, Flasch A, Roman RJ, White JA](#). [Related Articles](#), [Links](#)



Distribution of cytochrome P-450 4A and 4F isoforms along the nephron in mice.

Am J Physiol Renal Physiol. 2003 Jan;284(1):F95-102. Epub 2002 Aug 27.

PMID: 12388424 [PubMed - indexed for MEDLINE]

☐ 7: [Christmas P, Jones JP, Patten CJ, Rock DA, Zheng Y, Cheng SM, Weber BM, Carlesso N, Scadden DT, Rettie AE, Sobernhan RJ](#). [Related Articles](#), [Links](#)



Alternative splicing determines the function of CYP4F3 by switching substrate specificity.

J Biol Chem. 2001 Oct 12;276(41):38166-72. Epub 2001 Jul 18.

PMID: 11461919 [PubMed - indexed for MEDLINE]

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Hypoxic pulmonary vasoconstriction is modified by P-450 metabolites.

Am J Physiol Heart Circ Physiol. 2000 Oct;279(4):H1526-33.  
PMID: 11009437 [PubMed - indexed for MEDLINE]

- ☐ **22:** Frisbee JC, Roman RJ, Falck JR, Linderman JR, Lombard JH. Related Articles, Links



Impairment of flow-induced dilation of skeletal muscle arterioles with elevated oxygen in normotensive and hypertensive rats.

Microvasc Res. 2000 Jul;60(1):37-48.

PMID: 10873513 [PubMed - indexed for MEDLINE]

- ☐ **23:** Hercule HC, Oyekan AO. Related Articles, Links



Cytochrome P450 omega/omega-1 hydroxylase-derived eicosanoids contribute to endothelin(A) and endothelin(B) receptor-mediated vasoconstriction to endothelin-1 in the rat preglomerular arteriole.

J Pharmacol Exp Ther. 2000 Mar;292(3):1153-60.

PMID: 10688635 [PubMed - indexed for MEDLINE]

- ☐ **24:** Parviz M, Bousamra M 2nd, Chammas JH, Birks EK, Presberg KW, Jacobs ER, Nelin LD. Related Articles, Links



Effects of chronic pulmonary overcirculation on pulmonary vasomotor tone.

Ann Thorac Surg. 1999 Feb;67(2):522-7.

PMID: 10197682 [PubMed - indexed for MEDLINE]

- ☐ **25:** Lombard JH, Kunert MP, Roman RJ, Falck JR, Harder DR, Jackson WF. Related Articles, Links

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Cytochrome P-450 omega-hydroxylase senses O<sub>2</sub> in hamster muscle, but not cheek pouch epithelium, microcirculation.

Am J Physiol. 1999 Feb;276(2 Pt 2):H503-8.

PMID: 9950851 [PubMed - indexed for MEDLINE]



26: [Harder DR](#), [Narayanan J](#), [Birks EK](#), [Liard JF](#), [Imig JD](#), [Lombard JH](#), [Lange AR](#), [Roman RJ](#). Related Articles, Links



Identification of a putative microvascular oxygen sensor.

Circ Res. 1996 Jul;79(1):54-61.

PMID: 8925569 [PubMed - indexed for MEDLINE]



27: [Harder DR](#), [Gebremedhin D](#), [Narayanan J](#), [Jefcoat C](#), [Falck JR](#), [Campbell WB](#), [Roman R](#). Related Articles, Links



Formation and action of a P-450 4A metabolite of arachidonic acid in cat cerebral microvessels.

Am J Physiol. 1994 May;266(5 Pt 2):H2098-107.

PMID: 8203608 [PubMed - indexed for MEDLINE]



28: [Zou AP](#), [Ma YH](#), [Sui ZH](#), [Ortiz de Montellano PR](#), [Clark JE](#), [Masters BS](#), [Roman RJ](#). Related Articles, Links



Effects of 17-octadecynoic acid, a suicide-substrate inhibitor of cytochrome P450 fatty acid omega-hydroxylase, on renal function in rats.

J Pharmacol Exp Ther. 1994 Jan;268(1):474-81.

PMID: 8301590 [PubMed - indexed for MEDLINE]

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## EAST Search History

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L5 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN  
AN 2005:563127 CAPLUS  
DN 143:108822  
TI Cytochrome P-450: a new target in the heart and coronary  
circulation  
AU Doggrell, S. A.  
CS School of Biomedical Sciences, University of Queensland, QLD,  
4072,  
Australia  
SO Drugs of the Future (2005), 30(3), 261-269  
CODEN: DRFUD4; ISSN: 0377-8282  
PB Prous Science  
DT Journal; General Review  
LA English  
AB A review. Cytochrome P 450 enzymes (CYPs) are present in the  
heart and  
coronary circulation. The activation of CYP2J2/3 to increase  
the production  
of epoxyeicosatrienoic acids (EETs) may be cardioprotective in  
cardiac  
ischemia and reperfusion. On the other hand, inhibition of  
CYP2C9 with  
cimetidine, or more selectively with sulfaphenazole, is  
cardioprotective



in the perfused rat heart. In a dog model of cardiac ischemia and reperfusion, inhibitors of CYP o-hydroxylases (e.g., CYP4A, CYP4F) reduce infarct size. Inhibition of selected CYPs as an approach to the treatment of myocardial infarction should therefore be further developed. The function of CYPs in the coronary artery and other blood vessels is varied and complex, and only just beginning to be elucidated. In the coronary artery, when nitric oxide (NO) bioavailability is inhibited, the activity of CYPs may be increased, with the production of vasodilatory EETs. Conversely, when CYP2C9 is inactivated in humans with coronary artery disease (CAD), acetylcholine-induced NO-mediated vasodilatation is enhanced. In the presence of CAD/oxidized LDL, the EET vasodilatory system may be inhibited. Drugs that target CYPs and/or EETs are thus expected to be useful in the elucidation of the role of this system, and may also have therapeutic utility.

RE.CNT 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 6 MEDLINE on STN DUPLICATE 1  
AN 2004095780 MEDLINE  
DN PubMed ID: 14634044  
TI Catalytic activity and isoform-specific **inhibition** of rat cytochrome **p450 4F** enzymes.  
AU Xu Fengyun; Falck John R; Ortiz de Montellano Paul R; Kroetz Deanna L  
CS Department of Biopharmaceutical Sciences, University of California, San Francisco, CA 94143-0446, USA.  
NC GM-25515 (NIGMS)  
GM-31278 (NIGMS)  
HL-53994 (NHLBI)  
P30 DK26743 (NIDDK)  
SO The Journal of pharmacology and experimental therapeutics, (2004 Mar) Vol. 308, No. 3, pp. 887-95. Electronic Publication: 2003-11-21. Journal code: 0376362. ISSN: 0022-3565.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals

EM 200404  
ED Entered STN: 20040302  
Last Updated on STN: 20040407  
Entered Medline: 20040406  
AB Arachidonic acid is omega-hydroxylated to  
20-hydroxyeicosatetraenoic acid  
(20-HETE), which has effects on vasoactivity and renal tubular  
transport  
and has been implicated in the regulation of blood pressure.  
Cytochrome  
p450 (p450) 4A isoforms are generally considered the major  
arachidonic  
acid omega-hydroxylases; however, little is known about the role  
of rat  
CYP4F isoforms in 20-HETE formation. The rat CYP4F isoforms,  
CYP4F1,  
CYP4F4, CYP4F5, and CYP4F6, were heterologously expressed in  
Escherichia  
coli, and their substrate specificity in fatty acid metabolism  
was  
characterized. Substrate-binding assays indicated that  
leukotriene B(4)  
(LTB(4)) and arachidonic acid bound CYP4F1 and CYP4F4 in a  
type-I manner  
with a K(s) of 25 to 59 microM, and lauric acid bound CYP4F4  
poorly.  
Reconstituted CYP4F1 and CYP4F4 catalyzed the  
omega-hydroxylation of  
LTB(4) with a K(m) of 24 and 31 microM, respectively, and CYP4F5  
had minor  
activity in LTB(4) metabolism. Importantly, CYP4F1 and CYP4F4  
catalyzed  
the omega-hydroxylation of arachidonic acid with an apparent  
k(cat) of 9  
and 11 min(-1), respectively. Lauric acid was a poor substrate  
for all of  
the CYP4F isoforms, and CYP4F6 had no detectable fatty acid  
omega-hydroxylase activity. The p450 omega-hydroxylase  
inhibitors  
17-octadecynoic acid, 10-undecynyl sulfate, and  
N-methylsulfonyl-12,12-  
dibromododec-11-enamide showed isoform-specific inhibition of  
CYP4F1- and  
CYP4F4-catalyzed omega-hydroxylation of arachidonic acid and  
potency  
differences between the CYP4A and CYP4F isoforms. These data  
support a  
significant role for CYP4F1 and CYP4F4 in the formation of  
20-HETE and  
identify p450 inhibitors that can be used to understand the  
relative  
contribution of the CYP4A and CYP4F isoforms to renal 20-HETE  
formation.

L5 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN  
 AN 2004:822150 CAPLUS  
 DN 141:378078  
 TI Inhibition of Cytochrome P450 $\omega$ -Hydroxylase A novel endogenous  
 cardioprotective pathway  
 AU Nithipatikom, Kasem; Gross, Eric R.; Endsley, Michael P.; Moore,  
 Jeannine  
 M.; Isbell, Marilyn A.; Falck, John R.; Campbell, William B.;  
 Gross,  
 Garrett J.  
 CS Department of Pharmacology and Toxicology, Medical College of  
 Wisconsin,  
 Milwaukee, WI, USA  
 SO Circulation Research (2004), 95(8), e65-e71  
 CODEN: CIRUAL; ISSN: 0009-7330  
 PB Lippincott Williams & Wilkins  
 DT Journal  
 LA English  
 AB Cytochrome P450s (CYP) and their arachidonic acid (AA)  
 metabolites have  
 important roles in regulating vascular tone, but their function  
 and  
 specific pathways involved in modulating myocardial  
 ischemia-reperfusion  
 injury have not been clearly established. Thus, the authors  
 characterized  
 the effects of several selective CYP $\omega$ -hydroxylase inhibitors  
 and a  
 CYP $\omega$ -hydroxylase metabolite of AA, 20-hydroxyeicosatetraenoic  
 acid  
 (20-HETE), on the extent of ischemia-reperfusion injury in  
 canine hearts.  
 During 60 min of ischemia and particularly after 3 h of  
 reperfusion,  
 20-HETE was produced at high concns. A nonspecific CYP  
 inhibitor,  
 miconazole, and 2 specific CYP $\omega$ -hydroxylase inhibitors,  
 17-octadecanoic acid (17-ODYA) and  
 N-methylsulfonyl-12,12-dibromododec-11-  
 enamide (DDMS), markedly inhibited 20-HETE production during  
 ischemia-reperfusion and produced a profound reduction in  
 myocardial infarct  
 size (expressed as a percent of the area at risk) (19.6 $\pm$ 1.7%  
 [control],  
 8.4 $\pm$ 2.5% [0.96 mg/kg miconazole], 5.9 $\pm$ 2.2% [0.28 mg/kg 17-ODYA],  
 and  
 10.8 $\pm$ 1.8% [0.40 mg/kg DDMS],  $P$ <0.05, resp.). Conversely,  
 exogenous  
 20-HETE administration significantly increased infarct size  
 (26.9 $\pm$ 1.9%,  
 $P$ <0.05). Several CYP $\omega$ -hydroxylase isoforms, which are known to

produce 20-HETE such as CYP4A1, CYP4A2, and CYP4F, were demonstrated to be present in canine heart tissue and their activity was markedly inhibited by incubation with 17-ODYA. These results indicate an important endogenous role for CYP $\omega$ -hydroxylases and in particular their product, 20-HETE, in exacerbating myocardial injury in canine myocardium.

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L5 ANSWER 4 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

AN 2004:288125 BIOSIS

DN PREV200400286882

TI Norepinephrine-induced phospholipase D activation is independent of

cytochrome P450 4A and 4F in aortic vascular smooth muscle cells.

AU Parmentier, Jean-Hugues [Reprint Author]; Malik, Kafait U  
CS Pharmacology, University of Tennessee, 874 Union Avenue, Memphis, TN, 38163, USA

jparmentier@utmem.edu

SO FASEB Journal, (2004) Vol. 18, No. 4-5, pp. Abst. 171.16.  
<http://www.fasebj.org/>. e-file.

Meeting Info.: FASEB Meeting on Experimental Biology:

Translating the

Genome. Washington, District of Columbia, USA. April 17-21, 2004. FASEB.

ISSN: 0892-6638 (ISSN print).

DT Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 16 Jun 2004

Last Updated on STN: 16 Jun 2004

AB Norepinephrine (NE) stimulates phospholipase D (PLD) activity via phospholipase A2-dependent arachidonic acid (AA) release in rabbit aortic

vascular smooth muscle cells (VSMC). Exogenous

20-hydroxyeicosatetraenoic

acid, an eicosanoid generated through the cytochrome P450 (CYP)

4A

pathway, stimulates PLD activity. This study was conducted to determine

if endogenous CYP4-derived AA metabolites act as intracellular mediators

of NE-induced PLD activation in VSMC. Rabbit VSMC CYP4A and CYP4F

isoforms were depleted with antisense oligonucleotides (ODN) treatment for

48 hours. CYP4A or CYP4F depletion did not inhibit

NE-induced PLD activation but rather enhanced to a similar degree (20%) basal as well as NE-induced PLD activity. The corresponding CYP4A and CYP4F sense ODN did not alter CYP levels and basal or NE-induced PLD activity. CYP4A inducers, fenofibrate (100  $\mu$ M) and Wy 14643 (10  $\mu$ M), inhibited (20%) the basal and NE-induced PLD activity. These data suggest that PLD activation is independent of the CYP4A/4F pathway and that a CYP4-derived AA metabolite(s) maintains an inhibitory effect on basal PLD activity in rabbit VSMC. (USPHS Grant-19134, NIH-HLBI and AHA-Southeast Affiliate).

L5 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN  
AN 2004:765629 CAPLUS  
DN 141:293982  
TI Cytochrome P450 4Fs: response and role following brain trauma  
AU Strobel, H. W.; Kalsotra, A.; Dash, P. K.  
CS Department of Biochemistry and Molecular Biology, The University of Texas-Houston Medical School, Houston, TX, USA  
SO Cytochromes P450: Biochemistry, Biophysics and Drug Metabolism, International Conference on Cytochromes P450, 13th, Prague, Czech Republic, June 29-July 3, 2003 (2003), Meeting Date 2003, 107-114.  
Editor(s): Anzenbacher, Pavel; Hudecek, Jiri. Publisher: Monduzzi Editore, Bologna, Italy.  
CODEN: 69FTSZ; ISBN: 88-323-3142-X  
DT Conference; (computer optical disk)  
LA English  
AB Following TBI, the expression of CYP4F proteins in lung, liver and kidney show tissue specific effects. CYP4F expression and associated LTB4  $\omega$  hydroxylase activity increase markedly in the lung, less markedly but significantly in the kidney while no change is observed in the liver. LTB4 degradation by CYP4F enzymes seems to be a central pathway involved in modulating inflammatory response after brain trauma.  
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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L5 ANSWER 6 OF 6 MEDLINE on STN DUPLICATE 2  
AN 2001256258 MEDLINE

DN PubMed ID: 11353747  
TI A novel cytochrome P450 enzyme responsible for the metabolism of ebastine in monkey small intestine.  
AU Hashizume T; Mise M; Matsumoto S; Terauchi Y; Fujii T; Imaoka S; Funae Y; Kamataki T; Miyazaki H  
CS Developmental Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Osaka, Japan.. takanori-hashidume@dainippon-pharm.co.jp  
SO Drug metabolism and disposition: the biological fate of chemicals, (2001 Jun) Vol. 29, No. 6, pp. 798-805.  
Journal code: 9421550. ISSN: 0090-9556.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200108  
ED Entered STN: 20010903  
Last Updated on STN: 20010903  
Entered Medline: 20010830  
AB Small intestinal microsomes of cynomolgus monkeys were found to catalyze hydroxylation and dealkylation of an H(1)-antihistamine prodrug, ebastine.  
To identify the main enzyme responsible for ebastine hydroxylation, which has been hitherto unknown, we purified two cytochrome P450 isoforms, named P450 MI-2 and P450 MI-3, from the intestinal microsomes on the basis of the hydroxylation activity. P450 MI-2 and P450 MI-3 showed the respective apparent molecular weights of 56,000 and 53,000 on sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The internal amino acid sequence of P450 MI-2 had high similarity with those of human CYP4F2, CYP4F3, and CYP4F8. The first 27 amino acid residues of P450 MI-3 were highly homologous with those of monkey CYP3A8 and human CYP3A4/5/7.  
Furthermore, P450 MI-2 and P450 MI-3 were recognized by anti-CYP4F and anti-CYP3A antibodies, respectively, in immunoblot analysis and catalyzed leukotriene B(4) omega-hydroxylation and testosterone 6beta-hydroxylation, which are known to be mediated by CYP4F and CYP3A, respectively. Although both enzymes had ebastine hydroxylation activity, the V(max) value of P450

MI-2 was much higher than that of P450 MI-3 (37.0 versus 0.406 nmol/min/nmol of P450), and the former K(M) (5.1 microM) was smaller than the latter K(M) (10 microM). Anti-CYP4F antibody **inhibited** the hydroxylation in small intestinal microsomes strongly (70%), but anti-CYP3A antibody did not. These results indicate that P450 MI-2 belongs to the CYP4F subfamily and is mainly responsible for hydroxylation of ebastine in monkey small intestinal microsomes. This suggests that the small intestinal CYP4F enzyme, P450 MI-2, can play an important role in the metabolism of drugs given orally.